Editorial

Editorial response to "Clinical complete response to neoadjuvant chemotherapy for muscle-invasive bladder cancer: contemporary outcomes of a multi-institutional cohort study"

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The ultimate goal of cancer therapy is to cure the patient and restore a high quality of life. For patients with muscle invasive bladder cancer (MIBC), the ability to preserve the bladder is an important goal since it will avoid the complications of cystectomy and long-term negative implications on urinary and sexual function. It has been recognized that transurethral resection of the bladder (TUR) alone can cure a select group of patients with MIBC who have relatively small tumors (<5 cm), no palpable mass, no hydronephrosis, no enlarged lymph nodes on imaging and complete TUR (1). However, these patients are rare and TUR alone is not recommended according to guidelines unless other options are not safe or patient refuses other therapy (2). In fact, the guidelines note that patients should be informed that up to 47% of patients treated in this manner still require cystectomy and have an increased risk of bladder cancer mortality. There is level 1 evidence that neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC) confers improved survival over cystectomy alone (3). In fact, patients in the methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) group had a 38% pT0 rate including 50% of patients who initially had cT2 disease. Naturally, these patients wonder if the cystectomy was necessary. The pertinent question is what would happen to the patient if the bladder was not removed and would it be worse than the 85% 5-year overall survival achieved in patients who underwent cystectomy and were found to be pT0.

The recently published retrospective study by Mazza *et al.* reviewed 148 patients with MIBC who underwent NAC and had a complete response (pT0) on post-NAC transurethral resection of bladder tumor (TURBT) who elected surveillance (4). At TURBT prior to NAC, most patients had a solitary cT2 tumor and only 29% had concomitant carcinoma in situ (CIS). Gemcitabine and cisplatin were used in 63% of the patients and at least 4 cycles were used in 81%. The 5-year disease-specific, overall, cystectomy-free, and recurrence-free survival rates were 90%, 86%, 76%, and 64% with 55-month median follow-up. Cancer recurred locally in 48% of the patients including 37% with non-MIBC (NMIBC) and 11% with MIBC. Salvage RC was used in 12 patients with MI recurrence and 14 patients with non-invasive recurrence of which 75% and 93% survived, respectively. In the study, there were 15 bladder cancer deaths of which 11 patients recurred in the bladder (4 MIBC and 7 NMIBC). The authors suggest that these 11 patients (7% of population) could have benefitted from an immediate RC. However, this assumes that all patients undergoing cystectomy would survive their operation.

A recent systematic review of the literature reported on outcomes of patients treated with TURBT and systemic chemotherapy as definitive treatment for locally confined MIBC (5). The review included 18 publications (518 patients) and there was also a meta-analysis performed including 10 publications (266 patients). There was a wide range of reported overall survival (20% to 87.5%) and significant variance in median follow-up (4 to 120 months). The meta-analysis found that 5-year survival rate was 72% (95% CI: 64–82%). There was limited

reporting on frequency of salvage cystectomy but the mean among studies that did report cystectomy rate found it was approximately 33% (range, 0–65%). There was too much heterogeneity to compare cisplatinum based regimens to those using carboplatinum-based regimens. Also there was variability in the quality of TUR among studies.

There are potential ways to improve results of NAC. A recent multicenter, retrospective study including 319 patients with cT3–4aN0M0 disease compared ypT0N0 between the gemcitabine and cisplatin, and dose dense MVAC regimens (6). The dose dense MVAC arm was more likely to result in ypT0N0 compared to the gemcitabine and cisplatin arm (28% *vs.* 14.6%, P=0.005). Furthermore, there are studies that have shown that markers including mutations in DNA repair genes *ATM*, *RB1*, and *FANCC* (7), mutations in excision repair cross-complementation group 2 gene (8), and RNA subtyping of bladder cancer (9) may improve prediction of response to platinum-based chemotherapy. With improved selection of patients and increased use of NAC and dose dense MVAC, it is likely that the percent of patients with pT0 disease will increase. As such it is important to have prospective trials to identify which patients may safely avoid cystectomy. While retrospective studies cannot tell us who will not recur, they do shed light on patients at higher risk who should have cystectomy. Patients with residual disease on TUR after NAC, palpable disease on bimanual exam, hydronephrosis and CIS are all at increased risk for recurrence and should likely be excluded from trials. There is also a need to improve imaging since pT0 patients are not by definition also node negative.

At this time, it appears that patients who inquire about keeping their bladder after NAC still need to be encouraged to undergo cystectomy (2). The data suggests that approximately 50% of patient will recur locally and 1/3 will undergo salvage cystectomy. Furthermore, even in highly selected patients who are pT0 after NAC, 7–16% will likely die of their disease (10). Clinical trials are necessary to determine whether select patients who are pT0 after NAC and repeat TUR can safely proceed with monitoring rather than undergo cystectomy. Outcomes for such trials should involve not only overall survival but also quality of life measures.

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Footnote

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